Amendments to the Specification:

Please replace the paragraph beginning at page 2, line 3, with the following:

--It has previously been reported that Activity Dependent Neurotrophic Factor (ADNF) polypeptides can be used to prevent or reduce neuronal cell death. Activity Dependent Neurotrophic Factor I (ADNF I) polypeptide is secreted by astroglial cells in the presence of vasoactive intestinal peptide (VIP). The ADNF I polypeptide exhibits survival-promoting activity for neurons at surprisingly low, femtomolar concentrations (Brenneman & Gozes, *J. Clin. Invest.* 97:2299-2307 (1996)). Further studies identified peptide fragments of ADNF I that mimic the neurotrophic and neuroprotective properties of ADNF I. The shortest peptide (*i.e.*, the active core site) that captured the survival-promoting activity of ADNF I was the peptide SALLRSIPA (SEQ ID NO:1), designated as ADNF-9 or SAL (Brenneman *et al.*, *J. Pharm. Exp. Therp.* 285:619-627 (1998)). Studies of related molecules to the ADNF I polypeptide resulted in the discovery of Activity Dependent Neuroprotective Protein (called ADNP or ADNF III interchangeably). This protein was cloned (Bassan *et al.*, *J. Neurochem.* 72:1283-1293 (1999)) and was found to have an active peptide similar in biological activity to SAL. This peptide (*i.e.*, the active core site) was NAPVSIPQ (SEQ ID NO:2), designated as NAP.--

Please replace the paragraph beginning at page 5, line 17, with the following:

--Figure 1 compares the survival-promoting activity of D- and L-forms of SALLRSIPA (SEQ ID NO:1) in dissociated cerebral cortical cultures treated with 1 μM tetrodotoxin, an agent that blocks electrical activity and produces apoptotic neuronal cell death. Treatment duration was for 5 days. Each point is the mean ± the standard error of 3-4 determinations. Neuronal cell counts were obtained without knowledge of the treatment group.--

Please replace the paragraph beginning at page 5, line 23, with the following:

--Figure 2A compares the survival-promoting activity of D- and L-forms of NAPVSIPQ (SEQ ID NO:2) in dissociated cerebral cortical cultures treated with 1 μM tetrodotoxin. Experimental conditions were as described for Figure 1.--

Please replace the paragraph beginning at page 5, line 26, with the following:

--Figure 2B illustrates the effect of a mixture of D- and L-amino acid D-NA{L-P}VSIPQ on survival promoting activity in cerebral cortical culture co-treated with tetrodotoxin for 5 days. In peptide NAPVSIPQ (SEQ ID NO:2), all of the amino acids were in the D-form, except the third proline residue was in the L-form.--

Please replace the paragraph beginning at page 5, line 30, with the following:

--Figure 3A compares the survival-promoting activity of combinations of NAPVSIPQ (SEQ ID NO:2) and SALLRSIPA (SEQ ID NO:1) in D- and L-forms. Experimental conditions were as described for Figure 1.--

Please replace the paragraph beginning at page 6, line 1, with the following:

--Figure 3B compares the survival-promoting activity of combinations of L-NAPVSIPQ (SEQ ID NO:2) + D-SALLRSIPA with D-NAPVSIPQ and L-SALLRSIPA (SEQ ID NO:1). Experimental conditions were as described for Figure 1.--

Please replace the paragraph beginning at page 9, line 22, with the following:

--The phrase "ADNF polypeptide" refers to one or more activity dependent neurotrophic factors (ADNF) that have an active core site comprising the amino acid sequence of SALLRSIPA (SEQ ID NO:1) or NAPVSIPQ (SEQ ID NO:2), or conservatively modified variants thereof that have neurotrophic/neuroprotective activity as measured with *in vitro* cortical neuron culture assays described by, *e.g.*, Brenneman *et al.*, *J. Pharmacol. Exp. Therp.* 285:629-627 (1998); Bassan *et al.*, *J. Neurochem.* 72:1283-1293 (1999). An ADNF polypeptide can be an ADNF I polypeptide, an ADNF III polypeptide, their alleles, polymorphic variants, or interspecies homolog, or any subsequences thereof, such as NAP and SAL, that exhibit neuroprotective/neurotrophic action on, *e.g.*, neurons originating in the central nervous system either *in vitro* or *in vivo*. An "ADNF polypeptide" can also refer to a mixture of ADNF I polypeptide and ADNF III polypeptide.--

Please replace the paragraph beginning at page 21, line 13, with the following:

--Because ADNF I and ADNF III polypeptides are neurotrophic factors, it was predicted that ADNF I and ADNF III polypeptides comprising D-amino acids would not be able to activate their respective stereoselective membrane receptors. Surprisingly, it was found that ADNF I and ADNF III polypeptides comprising D-amino acids were bioactive. In fact, all D- and all L-amino acid forms of the active core site peptide from ADNF I polypeptides, *i.e.*, SALLRSIPA (SEQ ID NO:1) (SAL), were virtually identical in neuronal survival activity *in vitro*. Similarly, all D- and all L-amino acid forms of the active core site peptide from ADNF III polypeptides, *i.e.*, NAPVSIPQ (SEQ ID NO:2) (NAP), were virtually identical in neuronal survival activity *in vitro*. It is very uncommon that all D-amino acid peptides are active, and even more uncommon that the D- and L-isomers of a given peptide are equally active.--

Please replace the paragraph beginning at page 26, line 7, with the following:

--Within the scope, certain ADNF I and ADNF III polypeptides are preferred, namely those in which x, y, w, and z are all zero (*i.e.*, SALLRSIPA (SEQ ID NO:1) and NAPVSIPQ (SEQ ID NO:2), respectively). Equally preferred are ADNF I polypeptides in which x is one; R^1 is Val-Leu-Gly-Gly-Gly (SEQ ID NO:5); and y is zero. Also equally preferred are ADNF I polypeptides in which x is one; R^1 is Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly (SEQ ID NO:6); and y is zero. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Gly-Gly; and z is zero. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Leu-Glu-Gly; z is one; and R^4 is Gln-Ser. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Leu-Gly-Leu-Gly-Gly- (SEQ ID NO:7); z is one; and R^4 is Gln-Ser. Also equally preferred are ADNF III polypeptides in which w is one; R^3 is Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly (SEQ ID NO:8); z is one; and R^4 is Gln-Ser. Additional amino acids can be added to both the N-terminus and the C-terminus of these active core sites (SALLRSIPA (SEQ ID NO:1) or NAPVSIPQ (SEQ ID NO:2)) without loss of biological activity as evidenced by the fact that the intact ADNF I or ADNF III growth factors exhibit extraordinary biological activity. *See*, U.S.S.N. 08/324,297, filed October 17, 1994 (also published as WO96/11948) for the description of ADNF I polypeptides; and U.S.S.N. 60/037,404 filed February 27, 1997 and U.S.S.N. 60/059,621 filed, September 23, 1997 (also published as WO98/35042) for the description of ADNF III polypeptides, all of which are incorporated herein by reference.--

Please replace the paragraph beginning at page 32, line 31, with the following:

--Small polypeptides including SALLRSIPA (SEQ ID NO:1) and NAPVSIPQ (SEQ ID NO:2) cross the blood brain barrier. For longer polypeptides that do not cross blood the brain barrier, methods of administering proteins to the brain are well known. For example, proteins, polypeptides, other compounds and cells can be delivered to the mammalian brain via

intracerebroventricular (ICV) injection or via a cannula (*see, e.g.*, Motta & Martini, *Proc. Soc. Exp. Biol. Med.* 168:62-64 (1981); Peterson *et al., Biochem. Pharmacol.* 31:2807-2810 (1982); Rzepczynski *et al., Metab. Brain Dis.* 3:211-216 (1988); Leibowitz *et al., Brain Res. Bull.* 21:905-912 (1988); Sramka *et al., Stereotact. Funct. Neurosurg.* 58:79-83 (1992); Peng *et al., Brain Res.* 632:57-67 (1993); Chem *et al., Exp. Neurol.* 125:72-81 (1994); Nikkhah *et al., Neuroscience* 63:57-72 (1994); Anderson *et al., J. Comp. Neurol.* 357:296-317 (1995); and Brecknell & Fawcett, *Exp. Neurol.* 138:338-344 (1996)). In particular, cannulas can be used to administer neurotrophic factors to mammals (*see, e.g.*, Motta & Martini, *Proc. Soc. Exp. Biol. Med.* 168:62-64 (1981) (neurotensin); Peng *et al., Brain Res.* 632:57-67 (1993) (NGF); Anderson *et al., J. Comp. Neurol.* 357:296-317 (1995) (BDNF, NGF, neurotrophin-3).--

Please replace the paragraph beginning at page 47, line 3, with the following:

--As shown in Figure 1, the D- and L-forms of SALLRSIPA (SEQ ID NO:1) (SAL) were identical in both potency and efficacy in preventing neuronal cell death associated with electrical blockade with TTX. Each point is the mean of at least three determinations, the error bars are the standard errors. Similarly, the D- and L-forms of NAPVSIPQ (SEQ ID NO:2) (NAP) were very similar, with each exhibiting a complex dose response with two apparent maxima (Figure 2A). Unless indicated as otherwise, L-SAL and D-SAL refer to a peptide having an amino acid sequence of Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala (SEQ ID NO:1) comprising all L-amino acids or all D-amino acids, respectively. Also, L-NAP and D-NAP refer to a peptide having an amino acid sequence of Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln (SEQ ID NO:2) comprising all L-amino acids or all D-amino acids, respectively.--

Please replace the paragraph beginning at page 47, line 13, with the following:

--In Figure 2B, the effect of an ADNF peptide that has amino acid residues in both L-form and in D-form, namely D-NA{L-P}VSIPQ, was tested. In this ADNF peptide, all

of the amino acids of NAPVSIPQ (SEQ ID NO:2) were in the D-form, except the third proline residue was in the L-form. Cerebral cortical cultures were treated with 1 μM TTX for 5 days, which is a model of apopotic death that is relevant to neurodegenerative disease. Cultures treated with the toxin were given various concentrations of D-NA{L-P}VSIPQ. As all L- and all D- amino acid NAPVSIPQ (SEQ ID NO:2), this mixed D/L peptide D-NA{L-P}VSIPQ retained survival-promoting activity and was effective in cell culture in preventing neuronal cell death in the TTX model.--

Please replace the paragraph beginning at page 50, line 9, with the following:

--Figures 10A and 10B illustrates effects of oral administration of ADNF polypeptides on pup brain weight and fetal death. Pregnant mice were injected with alcohol as a model for fetal alcohol syndrome according to methods of Webster et al. (1980), *supra*. The pregnant mice were injected 25% alcohol at 0.030 ml/g body weight. Peptide was dissolved in phosphate-buffered saline and administered orally by gavage 30 minutes prior to alcohol treatment. D-SAL (all D-amino acids of SALLRSIPA (SEQ ID NO:1)) at 40 μg was found to prevent fetal death as assessed on E18.--

Please replace the paragraph beginning at page 53, line 15, with the following:

--Figure 14C illustrates the effect of oral administration of D-SALLRSIPA alone on learning and memory in rats treated with the cholinotoxin AF-64A. Rats were treated with the cholinotoxin AF-64A and D-SALLRSIPA as described in Gozes et al., *J. Pharmacol. Exp. Therap.* 293: 1091-1098 (2000), except that D-SALLRSIPA was delivered to AF64A-treated rats was as follows: 10 microgram D-SALLRSIPA (D-SAL) per rat (250-300 g) per day in 50 microliter saline under the tongue, using a micropipette. Peptides were applied once daily for three days, a week after the AF64A lesion. After a 2-day cessation, peptides were applied once daily for another 5 days and tested from day three on. Following an additional two-day

cessation, peptides were applied again daily for two days and tested in the Morris water maze. The graph shows the results of the 5 day testing. In each day the animals were subjected to two consecutive tests and results are a summation of the two daily tests. Significance (one way ANOVA with Student-Neuman-Kuels multiple comparison of means test) is as follows.

Day 1: $P < 0.04$ D-SALLRSIPA-AF64A vs. AF64A;

Day 2: $P < 0.04$ AF64A vs. control (sham operated), SALLRSIPA (SEQ ID NO:1) treatment was not significantly different from either AF64A animals or control, suggesting some improvement;

Day 3: No difference;

Day 4: No difference; and

Day 5: t-test: $P < 0.04$ D-SALLRSIPA-AF64A vs. AF64A.

These results suggest that D-SALLRSIPA (D-SAL) is effective on its own.--

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1-6, at the end of the application.